Accessing the antipodal series in microbial arene oxidation: a novel diene rearrangement induced by tricarbonyliron(0) complexation†

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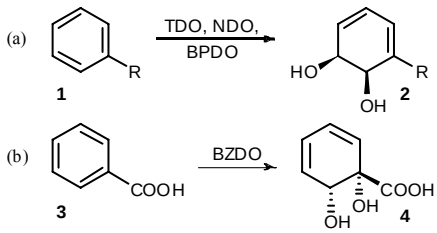
Received (in XXX, XXX) Xth XXXXXXXXX 200X, Accepted Xth XXXXXXXXX 200X

First published on the web Xth XXXXXXXXX 200X

DOI: 10.1039/b000000x

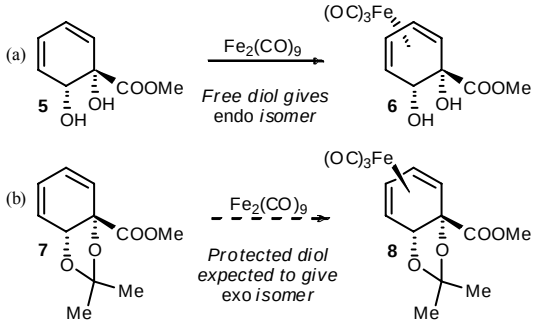
A cyclohexadiene ligand prepared by microbial arene 1,2-dihydroxylation undergoes spontaneous rearrangement upon complexation to tricarbonyliron(0). Subsequent iron removal affords a novel route to formal arene 2,3-dihydroxylation products enantiomeric to those obtainable by direct microbial arene oxidation.

Since the first report in 1968,[1] enzymatic dihydroxylation of aromatic substrates to afford enantiopure building blocks for synthesis has become established methodology.[2] In excess of 400 arene *cis*-diol products have been reported. The vast majority of these are produced by organisms expressing toluene dioxygenase (TDO), naphthalene dioxygenase (NDO) and biphenyl dioxygenase (BPDO) enzymes. These metabolise substituted arene substrates in a regio- and stereoselective fashion. A reliable predictive model has been reported for such transformations[3] and the sense of enantioinduction is conserved across organisms and substrates (Scheme 1a). In contrast, organisms expressing benzoate dioxygenase (BZDO) enzymes oxidise benzoic acids in a process that exhibits not only different regioselectivity, but also the opposite sense of enantioinduction. For example, *R. eutrophus* B9,[4] *P. putida* U103[5] and *P. putida* KTSY01 (pSYM01)[6] oxidise benzoic acid to benzoate 1,2-*cis* dihydrodiol **4** (Scheme 1b). Diol **4** has proved to be a versatile chiron for synthesis, having seen several applications,[7] most notably in the synthesis of tetracycline antibiotics.[8]



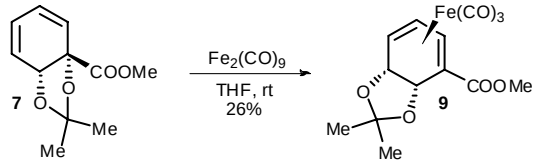
Scheme 1. Regio- and stereoselectivity of dioxygenases.

Dienes such as **2** and **4** may be derivatised as the corresponding tricarbonyliron(0) complexes[9] and we have recently shown that the methyl ester of **4** coordinates to iron with complete facial selectivity.[10] The sole isomer obtained is that in which the diol is *endo* (**6**, Scheme 2a), which is noteworthy since the diene presents Lewis basic functionality on both faces. Coordination to iron permits stereoselective ligand modification at the carbons adjacent to the diene, by means of cationic η^5-dienyl intermediates.[11] In this context we sought to access a complex in which the diol was *exo*, by protecting the diol as an acetonide (Scheme 2b). We reasoned that additional steric bulk on the lower face would disfavour the precoordination of the iron to a Lewis basic diol oxygen lone pair, which has been proposed to rationalise the facial selectivity observed previously.



Scheme 2. Lewis basic functionality directs iron coordination.

In the event, treatment of acetonide **7** with $Fe_2(CO)_9$ in THF gave **9**, in which the acetonide was indeed *exo*, but an isomerisation had occurred such that the ester was now conjugated to the diene (Scheme 3). The structure of **9** was determined by X-ray crystallography (Figure 1).[12]



Scheme 3. Diene rearrangement upon complexation.

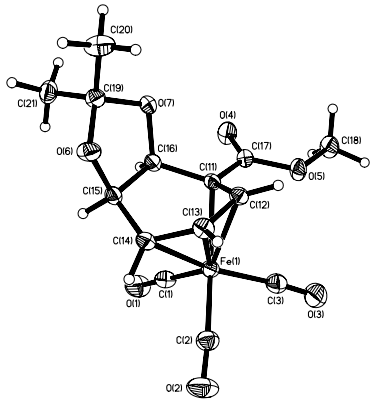
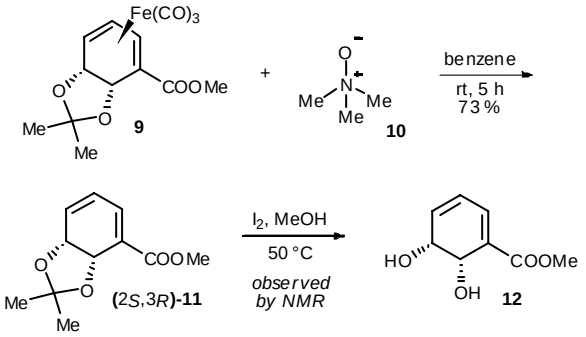


Fig. 1. X-Ray structure of **9**. (50% Thermal ellipsoids for all non-hydrogen atoms).

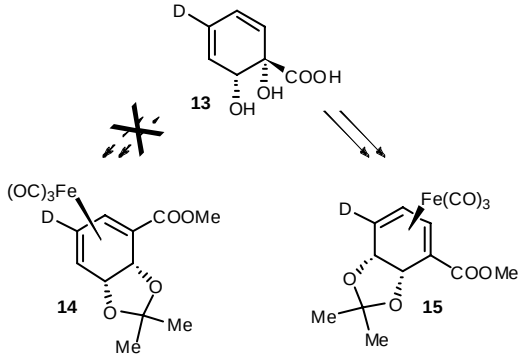
Isomerised complex **9** underwent facile oxidative

demetallation with trimethylamine *N*-oxide to afford uncomplexed diene (2*S*,3*R*)-**11** (Scheme 4). The enantiopurity of (2*S*,3*R*)-**11** was determined to be >95% *e.e.* by means of ester reduction and subsequent formation of Mosher's ester derivatives.‡ Attempted removal of the acetonide in (2*S*,3*R*)-**11** upon exposure to Brønsted acid proved unsuccessful due to facile dehydration/rearomatisation. However, in preliminary experiments, iodine in methanol[13] has been observed by NMR to afford **12** from (2*S*,3*R*)-**11**, albeit with a degree of concomitant rearomatisation.



Scheme 4. Deprotection of **9**.

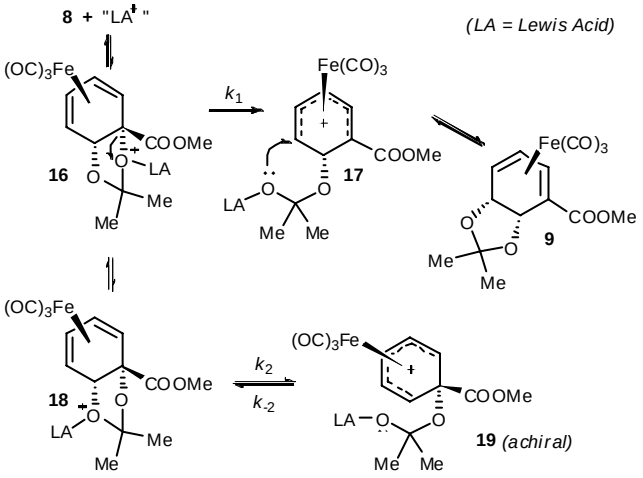
Direct microbial oxidation of methyl benzoate to afford a 2,3-diol and subsequent acetonide formation has been reported.[14,15] However, in this instance, the opposite enantiomer, (2*R*,3*S*)-**11** was obtained. Indeed, the enantiomer reported here, (2*S*,3*R*)-**11**, has not been described to date; this iron-mediated diene rearrangement represents a new route to an arene 2,3-*cis* diol derivative *antipodal to that obtained by direct biooxidation*. Thus far, the synthetic utility of arene 2,3-*cis*-diols has been constrained by the comparative difficulty in accessing the non-natural enantiomeric series. We anticipate that the transformation reported here will be of great synthetic utility, for example in allowing the synthesis of D-configured carbasugars (many L-carbasugars have been synthesised from diols of type **2**; the synthesis of (2*S*,3*R*)-**11** reported here constitutes formal syntheses of carba-β-D-galactopyranose, carba-β-D-talopyranose and carba-α-D-talopyranose[15]). In addition, elaboration of the ester will permit access to numerous antipodal arene 2,3-*cis* diols not accessible by other means.



Scheme 5. Isotopic labelling of substrate confirms acetonide migration.

As regards the mechanism of formation of **9**, isotopic labelling studies were undertaken to ascertain the identity of the migrating group. Biooxidation of *para*-deuterobenzoic afforded **13**, which then permitted the preparation of **15** (Scheme 5). Regioisomer **14** was not formed, confirming that **9** arises through migration of the acetonide and not the carboxymethyl group.

In view of the above, a mechanism may be proposed that invokes an intermediate cationic η^5-cyclohexadienyl intermediate,[11] **17**. This could plausibly arise from initial formation of the expected 1,2-isomer **8**, subsequent co-ordination of an unspecified Lewis-acidic species to an acetonide oxygen and C–O bond scission. Attack of the tethered nucleophile (*exo* to iron and ω- to the electron-withdrawing group, as is precedented[16]) would then generate **9** (Scheme 5). In addition to **17**, the regioisomeric η^5 cation **19** may also be formed as a transient intermediate by means of C–O bond scission at the other acetonide oxygen. The two cations **17** and **19** differ appreciably in electronic structure as the ester is conjugated to the dienyl system only in **17**. Crucially, **19** is achiral; recombination of the tethered nucleophile at either terminus of the η^5 dienyl ligand in **19** will effect racemisation of **8**.[17] That (2*S*,3*R*)-**11** and, by inference, **9** are not in fact racemic is suggestive of the reaction being under kinetic control. Specifically, formation of **17** may be kinetically favoured over **19** due to relief of steric strain as the ester α-carbon rehybridises such that the ester is in the plane of the dienyl system. If formation of **17** from **16** is effectively irreversible (due to the aforementioned preference for nucleophile recombination ω- to the ester) and $k_1 >> k_2$ (Scheme 6), the *e.e.* of **9** will not be eroded.



Scheme 6. Possible formation of **9** via cationic η^5-dienyl intermediate.

Variable temperature $^{13}C\{^1H\}$ NMR spectra for the carbonyl region of complex **9** clearly show fluxional behaviour. This fluxionality may be ascribed to turnstile rotation of the iron carbonyl ligands. The variable temperature spectra of **9** were simulated‡ in order to derive the activation parameters for the exchange process of E_a = 46.8 ±1.7 kJ mol^{-1}, $\Delta H^{\ddagger}$ = 44.4 ±1.6 kJ mol^{-1}, $\Delta S^{\ddagger}$ = -22.8 ±5.2 J K^{-1} mol^{-1} and $\Delta G^{\ddagger}_{(298)}$ = 51.2 ±3.1 kJ mol^{-1}. Use of $^{13}C\{^1H\}$ VT-NMR to probe fluxionality in tricarbonyliron(0) complexes is well established and thermodynamic parameters have been derived

by this method for numerous other tricarbonyliron(0)diene complexes.[18,19] The calculated value of $\Delta G^{\ddagger}_{(298)}$ for **9** is comparable to that for the analogous tropone complex ($\Delta G^{\ddagger}_{(298)}$ = 53.1 ±2.1 kJ mol^{-1}).[18]

In summary, we have defined a rearrangement route to arene 2,3-*cis* diol derivatives of non-natural configuration. The complex through which this rearrangement is realised exhibits hindered ligand rotation, for which thermodynamic data are presented. Our approach is complementary to other strategies reported previously for achieving this "enantiomeric switch". For example, substituted iodobenzenes can undergo 2,3-dihydroxylation followed by reductive iodine removal,[20,22] but this can preclude the use of diol derivatives possessing reductively labile functionality. The conceptually distinct approach of enantiodivergent synthesis has also been employed,[21,22] requiring that two different synthetic routes be established. In contrast, the approach we describe utilises only oxidative conditions and will permit access to both enantiomers of a given target by the same synthetic pathway. Investigations to elucidate further the mechanism of formation of **9** and to demonstrate the scope of this transformation are underway in our laboratory and will be reported in due course.

We thank Prosidion Limited, EPSRC and CIKTN for a CASE studentship (to MAK). We also thank Prof. Andrew G. Myers (Harvard) for a generous gift of *R. eutrophus* B9 cells.

Notes and references

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† This article is part of the 'Emerging Investigators' themed issue for *ChemComm*.

‡ Electronic Supplementary Information (ESI) available: Synthesis and characterisation of Mosher's esters. Details of NMR lineshape analysis. Experimental procedures and spectra. Crystallographic data for **9** (CCDC 768284). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

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